PATENT COOPERATION TREATY

17 DEC 2004

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

VOSSIUS & PARTNER
Siebertstrasse 4
D-81675 München
ALLEMAGNE

EINGEGANGEN
Vossius & Partner
04. Okt. 2004
Frist bearb.: lg

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	01.10.2004
Applicant's or agent's file reference: H 1978 PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/06551	20.06.2003	19.06.2002

Applicant: MAX-DELBRÜCK-CENTRUM FÜR MOLEKULARE MEDIZIN et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Nielsen-Hannerup, A

Tel. +49 89 2399-7739

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference H 1978 PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/06551	International filing date *(day/month/year)* 20.06.2003	Priority date *(day/month/year)* 19.06.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/4184		
Applicant MAX-DELBRÜCK-CENTRUM FÜR MOLEKULARE MEDIZIN et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22.12.2003	01.10.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Hornich, E Telephone No. +49 89 2399-8721

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/06551

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-10 as originally filed

Claims, Numbers

1-18 received on 08.06.2004 with letter of 07.06.2004

Drawings, Sheets

1-4 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-9 .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	9
	No:	Claims	1-8
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-9
Industrial applicability (IA)	Yes:	Claims	1-9
	No:	Claims	

2. Citations and explanations

see separate sheet

SECTION IV

1.1 The present application contains ***8 separate inventions*** which are not so linked as to form a *single general inventive concept* (**R. 13.1 PCT**):

The *problem* underlying the present application is the *provision of* new agents suitable for the treatment of acute or chronic pain, in particular of *allodynia* and *hyperalgesia*.

The *solution* of the present application resides in the provision of a pharmaceutical composition for the treatment of acute and / or chronic pain comprising

(i) *calcium channel blockers* which are capable of blocking voltage-dependent calcium channels (claim 1)

(ii) *calcium channel blockers* which are capable of blocking voltage-dependent calcium channels and *additionally one other pain killer* (claim 10).

The *common linking feature* of the pharmaceutical compositions defined under ***(I)*** and ***(ii)*** appears to be *calcium channel blockers*.
Pharmaceutical compositions comprising calcium channel blockers are known (see e.g. Eur. J. Clin. Pharmacol. (1999), 55: 559-565 and 'novelty').
Calcium channel blockers are furthermore known to be suitable for the treatment of pain (see US5929122; Pain 93 (2001); US6358706).

Thus, the compositions defined under ***(i)*** and ***(ii)*** *lack any common linking concept*.

The pharmaceutical compositions defined under ***(i)*** and ***(ii)*** thus represent ***two*** *separate inventions*:

(i) Invention 1: claims 1-9
(ii) Invention 2: claims 10-18

Furthermore, as regards *invention 2* ***(ii)***, pharmaceutical compositions comprising *calcium channel blockers* which are capable of blocking voltage-dependent calcium channels and *additionally one other pain killer* have as well already been described in the state of the art (see e.g. US5929122).

Thus, there is *no common linking concept* between the different groups of '*pain killers*'

mentioned in claim 11 which can be added to the pharmaceutical compositions comprising the *calcium channel blockers.*
Thus, each of the pharmaceutical compositions comprising *calcium channel blockers* which are capable of blocking voltage-dependent calcium channels in combination with

- ***(a)*** a NSAID (claims 10 (part), 11 (part), 12, 18 (part)),
- ***(b)*** a 5-HT_{1D} agonist (claims 10 (part), 11 (part), 13, 18 (part)),
- ***(c)*** a dopamin D_2 receptor antagonist (claims 10 (part), 11 (part), 14, 18 (part))
- ***(d)*** a secale alcaloid (claims 10 (part), 11 (part), 15, 18 (part))
- ***(e)*** a beta-blocker (claims 10 (part), 11 (part), 16, 18 (part)),
- ***(f)*** a calcium-channel blocker (claims 10 (part), 11 (part), 17, 18 (part)),
- ***(g)*** a neurokinin antagonist (claims 10 (part), 11 (part), 18 (part))

represents a separate invention.

The pharmaceutical compositions comprising *calcium channel blockers* and any of a compound encompassed by ***(a)*** - ***(g)*** thus represent ***seven*** *separate inventions.*

The application thus contains *eight separate inventions*.

1.2 As the Applicant has had a search report drawn up only for the first invention, examination concerning *novelty*, *inventive step* and *industrial applicability* is carried out for *Invention 1* relating to claims 1-9 (***R. 68.4*** and ***Art. 34(3)(c) PCT***).

SECTION V

2. *References:*

D1: KRAYENBUHL J C ET AL: "Drug-drug interactions of new active substances: Mibefradil example" EUROPEAN JOURNAL OF CLINICAL PHARMACOLOGY, vol. 55, no. 8, October 1999 (1999-10), pages 559-565, ISSN: 0031-6970

D2: US6358706

D3: DOGRUL A ET AL: "L-type and T-type calcium channel blockade potentiate the analgesic effects of morphine and selective [mu] opioid agonist, but not to selective [delta] and [kappa] agonist at the level of the spinal cord in mice" PAIN 2001 NETHERLANDS, vol. 93, no. 1, 2001, pages 61-68, ISSN: 0304-3959.

D4: US-A-5 929 122

D5: EP-A-1 312 362

D6: MUTH J N ET AL: "Use of transgenic mice to study voltage-dependent Channels" TRENDS IN PHARMACOLOGICAL SCIENCES, ELSEVIER TRENDS JOURNAL, CAMBRIDGE, GB, vol. 22, no. 10, 1 October 2001 (2001-10-01), pages 526-532, ISSN: 0165-6147.

D7: ANGUS J A ET AL: "Targeting voltage-gated calcium channels in cardiovascular therapy" LANCET, XX, XX, vol. 356, no. 9238, 14 October 2000 (2000-10-14), pages 1287-1289, ISSN: 0140-6736.

D5 was *published between the priority date and the filing date* of the present application.
On the assumption that the ***priority*** of the present application has been ***validly claimed***, **D5** is presently *not considered prior art* (R. 33.1 and 64.1 PCT).

D5 discloses that calcium channel inhibitors (mibefradil) are effective in the treatment of pain.

3. *Novelty* **(Art. 33(2) PCT)**

3.1 The subject-matter of claim 1 and the dependent claims 2-9 relates to a pharmaceutical composition *for the topical administration* for the treatment of acute and/or chronic pain comprising calcium channel blockers which are capable of blocking voltage-dependent calcium channels.
Calcium channel blockers which are capable of blocking voltage-dependent calcium channels are well-known compounds used in medicine (see for instance mibefradil, **D1** or the dihydropyridine derivatives made reference to on p. 3, last paragraph of the description; **D2-D4, D7**).
In interpreting claims for determining novelty, non-distinctive characteristics of a particular *intended use* are disregarded. Thus, the subject-matter of claims 1-9 discloses nothing more than the pharmaceutical composition suitable for the topical administration per se.

Pharmaceutical compositions comprising calcium channel blockers which are capable of blocking voltage-dependent calcium channels are already extensively used in medicine; the topical or nasal administration is for instance disclosed in **D2**, col. 20, l. 14-16, col. 21, l. 9-15, col. 22, l. 17-26.

Thus, **D2** would ***anticipate*** the subject-matter of claims 1-7.

D3 discloses amlodipine besylate and mibefradil dihydrochloride dissolved in saline and would therefore ***anticipate*** the subject-matter of claims 1-7.

D4describes the intranasal and local administration of calcium channel antagonists (see col. 2, l. 31 ff, e.g. dihydropyridines); 'solutions, ..., sprays are suitable for parenteral and topical administration and for administration by inhalation' (col. 2, l. 59-66). The subject-matter of claims 1-8 would thus be ***anticipated*** by **D4.**

3.2 Particular attention is furthermore drawn to documents **D2**, **D3** and **D4**:
D2 discloses the calcium channel blocker mibefradil and describes that '*selective suppression of the T channels will decrease neuronal hyperexcitability (painful neuropathies) and raise the treashold for the perception of pain (central pain syndromes)*' (col. 4, l. 7-11; col. 5, l. 24-39).

D3 and **D4** disclose that calcium antagonists (e.g. mibefradil, amlodipine) potentiate the analgetic effect of opioid agonists. **D4** discloses a composition comprising tramadol and a calcium antagonist suitable for the treatment of pain.

3.3 The subject-matter of claims 1-8 can thus **not** be considered **novel**.

4. *Inventive Step* **(Art. 33(3) PCT)**

The subject-matter of claim 9 merely relates to further ingredients for formulations; determination of *suitable formulations* would be a *matter of routine optimization* and would thus ***not involve*** an inventive step.

5. *Industrial Applicability* **(Art. 33(4) PCT)**

The requirements of industrial applicability would be fulfilled for the subject-matter of claims 1-9.

AMENDED CLAIMS SET 07. Juni 2004

1. Pharmaceutical composition for the topical administration for the treatment of acute and/or chronic pain comprising calcium channel blockers which are capable of blocking voltage-dependent calcium channels.

2. Pharmaceutical composition as defined in claim 1 wherein the calcium channel is a T-type or L-type channel.

3. Pharmaceutical composition as defined in claim 1 or 2 for the treatment of allodynia or hyperalgesia.

4. Pharmaceutical composition according to any one of claims 1 to 3 wherein the calcium channel blocker is mibefradil, its pharmaceutically acceptable analogues, salts or esters or a dihydropyridine.

5. Pharmaceutical composition for the treatment of pain associated with rheumatoid arthritis, cancer, injuries, back pain, herpes zoster and post-operative pain.

6. Pharmaceutical composition according to any one of claims 1 to 5 for the inhalative or intranasal administration.

7. Pharmaceutical composition according to claim 6 in form of an ointment, gel, crème or a solution or suspension, or plaster.

8. Pharmaceutical composition according to claim 6 in form of a nasal spray or inhalator.

9. Pharmaceutical composition according to any one of claims 1 to 3 characterised in that the drug form used is formed of biologically utilizable or

biodegradable substances wherein the biological materials are proteins or proteides, lipids or lipoids, carbohydrates or polysaccharides or mixtures of several of such materials.

10. Pharmaceutical composition according to any one of claims 1 to 3 characterised in that additionally one other pain killer is used.

11. Pharmaceutical composition according to claim 12 characterised in that the pain killer used in combination is an NSAID, a $5HT_{1D}$ agonist, a dopamin D_2 receptor antagonist, a secale alcaloid, a beta blocker, a calcium channel blocker or a neurokinin antagonist.

12. Pharmaceutical composition according to claim 12 characterised in that the NSAID is ibuprofen, meoxicam, indomethacin or naporxen.

13. Pharmaceutical composition according to claim 12 characterised in that the $5HT_{1D}$ agonist is sumatriptan, MK-452, naratriptan or 311C.

14. Pharmaceutical composition according to claim 12 characterised in that the dopamin D_2 receptor antagonist is metoclopramid.

15. Pharmaceutical composition according to claim 12 characterised in that the secale alcaloid is ergotamin, dihydroergotamin or metergolin.

16. Pharmaceutical composition according to claim 12 characterised in that the beta blocker is propranolol or metoprolol.

17. Pharmaceutical composition according to claim 12 characterised in that the calcium channel blocker is flunarizin or lomerizin.

18. Pharmaceutical composition according to claim 12 characterised in that the pain killer to be administered in combination is acetylsalicylic acid, paracetamol, clonidin, methysergid, dotarizin, lisurid, pizotifen, valproat, aminotraptilin CP-122,288 or UK 116,044.